Scientists uncover trigger to fatal neurodegenerative disease

June 22 2011

University of Tennessee researcher uses computer simulation to pinpoint changes in molecular structure that leads directly to disease.

Jeremy Smith, Governor's Chair for Molecular Biophysics at the University of Tennessee, Knoxville, has helped reveal a key trigger of Gerstmann–Sträussler–Scheinker (GSS) syndrome, a rare but deadly neurodegenerative disease. The finding could have far-reaching implications for the treatment of other neurodegenerative diseases such as Alzheimer's, Huntington's, and Parkinson's.

Smith conducted his research with two collaborators in Italy: Isabella Daidone, a former postdoctoral researcher of his who is now at the University of L'Aquila, and Alfredo Di Nola of the University of Rome "La Sapienza."

Most GSS patients begin developing symptoms in their late fifties. Symptoms include loss of memory, difficulty speaking, and unsteadiness and lead to progressive dementia, and then death within a few months or years. There is presently no cure or treatment. The disease results from a single, tiny mutation in a protein, resulting in it having a wrong shape—through "misfolding"—then aggregating to form amyloid plaques in the brain.

"Ever since the 'mad cow' scare in Britain in the 1990s, which led to several hundred human deaths and 4.4 million cattle being destroyed, I've been interested in finding out more about these fascinating diseases

of wrongly-shaped proteins," said Smith, who was born in England.

The team compared high-performance computer simulations of the structures of the normal and the GSS–mutant proteins. They found the GSS protein looks dramatically different from the normal form and revealed how its shape is primed for plaque formation.

"This research shows how computer simulation can be used to pinpoint changes in molecular structure that lead directly to disease," said Smith. "We think that a similar line of investigation should prove beneficial in understanding the origins of other amyloid diseases such as Alzheimer's, Parkinson's, and rheumatoid arthritis. Once the origin is understood at molecular detail, strategies to rationally prevent and cure a disease can be conceived."

The findings can be found in the article, "Molecular Origin of Gerstmann–Sträussler–Scheinker Syndrome: Insight from Computer Simulation of an Amyloidogenic Prion Peptide" in this month's edition of the *Biophysical Journal*.

Provided by University of Tennessee at Knoxville